Gastroesophageal Cancer

Leptomeningeal Carcinomatosis as the Only Manifestation of Disease in Recurrent Gastroesophageal Cancers

Syed Rizvi, Salman Fateh, Kamal K. S. Abbi, Yixing Jiang

Penn State Hershey Cancer Institute, Penn State College of Medicine, Hershey, PA

Meningeal carcinomatosis is characterized by diffuse spread of a cancer to the leptomeninges via cerebrospinal fluid. It is a rare condition that is seen more commonly with breast cancer, lung cancer, malignant melanoma, leukemias, and large cell lymphomas.[1,2] Gastric cancer is a less common cause of leptomeningeal carcinomatosis. Only handful of cases have been reported in the literature.

Leptomeningeal carcinomatosis caused by gastroesophageal cancer can present as part of the initial clinical presentation or during late metastatic disease. Diagnosis is often difficult to establish. Presence of malignant cells in the cerebrospinal fluid (CSF) is considered diagnostic.[3] Prognosis is generally poor, and median survival of gastric cancer patients with meningeal carcinomatosis is approximately 6 weeks.[4] In this article, we report two cases of recurrent gastric cancer that presented with leptomeningeal disease as the only relapse site.

CASE REPORT 1

A 55-year-old man presented with postprandial abdominal pain but no dysphagia in May 2007. He was initially treated with antacids, which did not improve his symptoms. In September 2007, he underwent upper endoscopy, which revealed a mass at the gastroesophageal junction and extensive involvement of gastric cardia and body. Biopsy confirmed poorly differentiated adenocarcinoma. Staging workup revealed no distant metastasis. He was treated with preoperative chemotherapy with DCF (docetaxel/cisplatin /5-fluorouracil), followed by total gastrectomy and distal esophagectomy.

Computed tomography (CT) and positron emission tomography (PET) studies revealed that he had responded well to treatment (Figure 1). Pathology of the surgical specimen revealed a residual T1N0 tumor. Postoperatively, he was offered adjuvant chemoradiotherapy. However, the patient declined radiotherapy. Because of the excellent response, the decision was made to give him two additional cycles of DCF. He completed his chemotherapy in May 2008.

In October 2008, he presented to the hospital with dysarthria. Magnetic resonance imaging (MRI) findings were suggestive of an ischemic stroke. The etiology was unclear, and the patient was discharged after he started recovering. Three and a half weeks later, he was admitted to the hospital with the same symptoms. Once again, MRI findings were suggestive of stroke. Subsequently, the patient developed nausea, diplopia, and headaches. A lumber puncture was performed. Analysis of the CSF showed atypical cells consistent with carcinoma. The patient deferred further treatment and was discharged to hospice.

CASE REPORT 2

A 49-year-old man developed dysphagia in August 2008. An upper gastrointestinal endoscopy revealed an ulcerating mass involving the distal esophagus and gastric cardia. A biopsy of the mass confirmed the diagnosis of adenocarcinoma. A PET scan performed in October 2008 showed fludeoxyglucose (18F) avid lymphadenopathy in the gastrohepatic ligament. He also underwent laparoscopic staging (at an outside institution) that did not reveal obvious abdominal metastasis. He was clinically staged as T3N1.

In November 2008, he underwent esophagectomy with gastric pull-through via minimally invasive surgery at an outside institution. Postoperative pathology was not available for review. A postoperative CT staging study showed a suspicious retroperitoneal lymphadenopathy. A fine needle biopsy was performed, and the cytology was positive for adenocarcinoma. Because of this finding, the patient was treated with systemic chemotherapy with DCF. He had complete radiographic response after two cycles of chemotherapy. He went on to receive additional cycles of chemotherapy.

The patient did well until June 2009, when he presented with frequent falls and intermittent headaches. CT and MRI studies of the brain showed no acute changes. On July 1, 2009, he was admitted to the hospital for generalized weakness and mental status changes. Repeat brain imaging again did not reveal acute abnormality. An electroencephalographic study was performed, which did not demonstrate epileptiform waves. On the second day of admission, his mental status improved as well as his weakness. On the third day of hospitalization, he developed blurred vision in the left eye and headaches. The patient had a history of migraine-like headaches, which often resolved with supportive measures. However, his headaches persisted, and his mental status waxed and waned.

A lumbar puncture was performed. Analysis of CSF showed low glucose and a high protein level consistent with malignancy. A final CSF cytology was positive for adenocarcinoma. The patient had leptomeningeal spread from his gastroesophageal cancer. His condition deteriorated quickly, and he died on the 12th day of admission.

DISCUSSION

Gastric cancer rarely progresses to leptomeningeal involvement. The incidence of leptomeningeal carcinomatosis related to gastro-

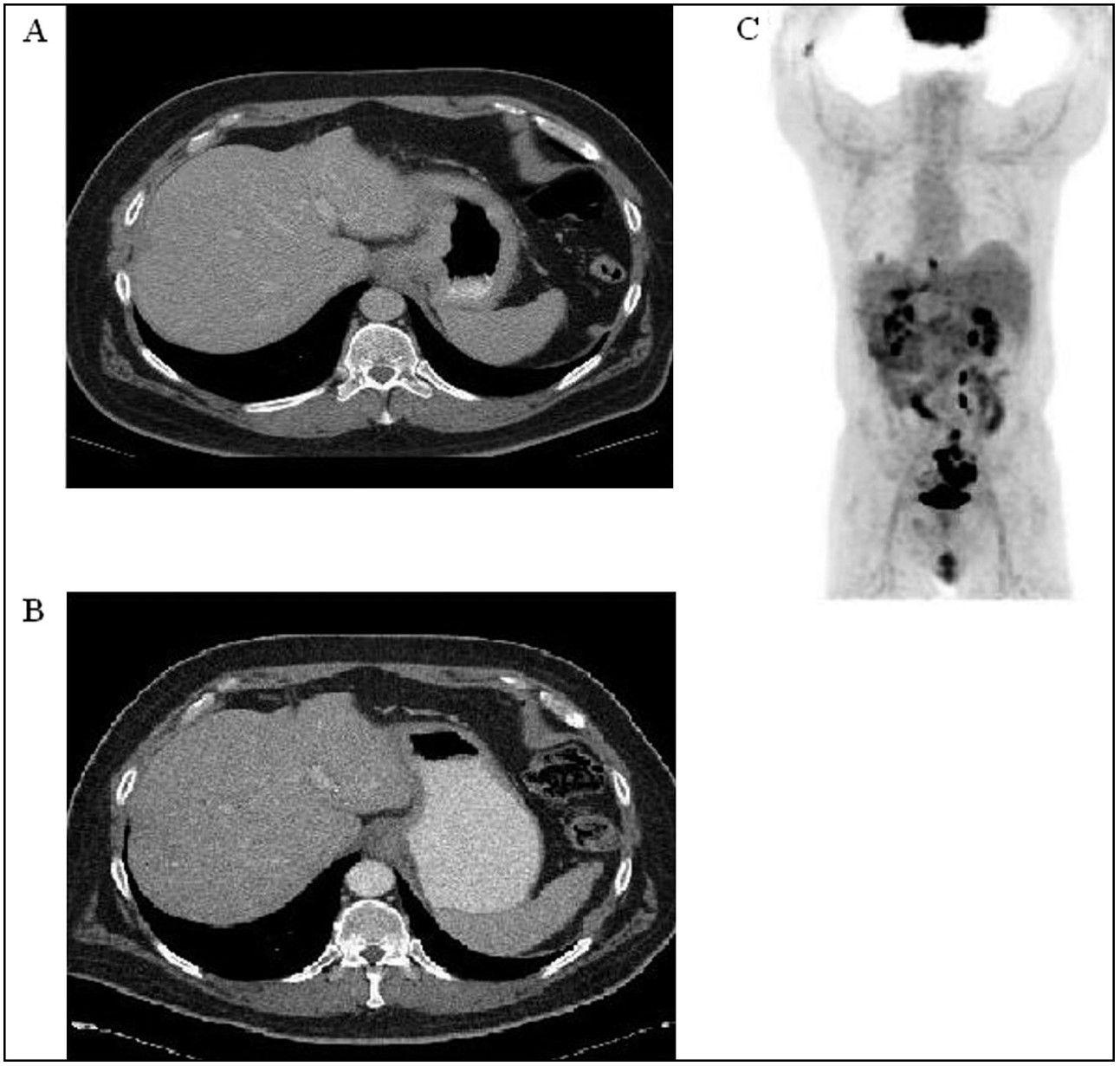

Figure 1. Imaging studies for case 1. (A) Pretreatment CT showed thickening of the GE junction with extensive gastric involvement (thickened gastric wall). (B) Postchemotherapy CT showed treatment response with decreased size of GE junction tumor and decreased thickening of the gastric wall. (C) Negative systemic disease demonstrated by PET at the time of CNS relapse.

esophageal cancer is approximately 0.17–0.19% as reported in the literature.[5,6] The clinical presentation is essentially similar to leptomeningeal disease caused by other adenocarcinomas. Table 1 summarizes potential routes by which meningeal spread may occur. Table 2 summarizes the clinical presentations of leptomeningeal carcinomatosis.

The diagnosis of leptomeningeal disease is often difficult, as some of the clinical symptoms are nonspecific and the disease itself is not always evident on imaging studies. MRI is commonly regarded as the imaging study of choice.[3] The sensitivity of MRI, however, varies from study to study. Sze et al reported a sensitivity of 66% in a group of 30 patients,[7] and Straathof et al reported 76% sensitivity and 77% specificity.[8] Gadolinium-enhanced T1 se-

Table 1. Routes of invasion of leptomeninges by cancerous cells*

1. Direct extension from the brain parenchyma
2. Hematogenous spread via the arachnoid vessels
3. Metastases to the choroid plexus and from there into the CSF
4. Extension from vertebral, subdural, or epidural metastases
5. Retrograde invasion along peripheral or cranial nerves to the subarachnoid space
6. De novo tumors arising in the meninges

*Gonzalez-Vitale et al 1976.

Table 2. Signs and symptoms of meningeal carcinomatosis*

Brain symptoms and signs	Headache Diabetes insipidus Encephalopathy (change in mental status)
Cranial nerve signs and symptoms	Diplopia Facial numbness Hearing loss Loss of visual acuity
Spinal signs and symptoms	Paraesthesias Leg weakness Neck or back pain Bladder and bowel dysfunction.

*Yamada et al 2008; Taillibert et al. 2005.

Table 3. Recommendations to minimize false negative results*

A minimum of 10 ml of CSF should be withdrawn with each sample solely for cytologic analysis
Specimens must be processed promptly, including immediate fixation in ethanol-based fixative for cytology
CSF should be obtained from a site of known leptomeningeal disease (ie, intraventricularly or by cervical spine puncture under fluoroscopic control for cranial symptoms and LP for spinal root dysfunction)
The ventricular puncture or LP should be repeated if the initial cytology is negative but clinical suspicion is high

*Yamada et al 2008; Haba et al 1983.

quences detect abnormal meningeal enhancement that is characteristic of leptomeningeal disease. Fluid-attenuated inversion recovery weighting may demonstrate increased signal of the sulci, reflecting abnormality in the subarachnoid space.[3] Contrast enhancement is not absolutely specific for leptomeningeal disease. However, in the appropriate clinical setting, it is highly suggestive.

Cytology of CSF is considered the gold standard in diagnosis. It is an invasive procedure, however, and sensitivity is suboptimal: false-negative results present a major problem. Wasserstrom et al reported a sensitivity of only 54% with a single lumbar puncture, though 91% sensitivity can be achieved with repeated tests.[2] Table 3 provides general guidelines to improve the diagnostic sensitivity.

Here we report two cases of meningeal carcinomatosis as the only site of disease recurrence. However, these two cases represent slightly differing clinical scenarios. In case 1, the patient completed systemic chemotherapy and was off treatment when he presented with meningeal disease in the absence of obvious systemic disease demonstrated by PET scan. The patient in case 2 was actively receiving DCF systemic chemotherapy when he developed meningeal disease. Unlike acute leukemia, it is not clear, biologically, what disposes a patient to develop meningeal disease in solid tumors. Clearly, the development of meningeal disease is independent of systemic tumor burden, ongoing systemic chemotherapy, and responsiveness to the chemotherapy.

Meningeal carcinomatosis is associated with a poor outcome. Lee et al reported a median survival of 4 weeks in patients with meningeal disease secondary to gastric carcinoma.[5] Steroids, radiotherapy, and intrathecal chemotherapy are the available treatment options. The treatment goals in patient with meningeal carcinomatosis are to improve the neurologic status and to prolong survival. High-dose steroids provide symptomatic relief, but the effects are short lived.[3] Radiotherapy can be considered for symptomatic relief.[9] Whole-brain irradiation is considered safe for patients with meningeal carcinomatosis.[2] The optimum treatment for symptomatic relief has not been well established, as data in the literature are limited.

Intrathecal chemotherapy is often used to treat meningeal carcinomatosis. However, the therapeutic benefit of this approach is still debatable, mainly because no consistent survival benefit has been demonstrated. Cytosine arabinoside (ara-C), methotrexate, and thiotepa are most commonly employed to treat leptomeningeal disease in gastric cancer.[10,11] Among these agents, methotrexate is the most frequently used. In some of the studies, however, it did not significantly affect survival of patients with leptomeningeal cancer secondary to gastric adenocarcinoma.[6,12] For example, Bokstein and coworkers prospectively randomized patients with leptomeningeal disease to either radiotherapy, intrathecal chemotherapy and systemic chemotherapy, or radiotherapy and systemic chemotherapy.[13] The addition of intrathecal chemotherapy did not improve overall survival but increased early treatment–related complications. On the other hand, some case series have shown reasonably prolonged survival with intrathecal chemotherapy.[2,3]

Kim and colleagues explored the efficacy of single-agent methotrexate versus combination methotrexate/ara-C in intrathecal chemotherapy.[14] The authors demonstrated that adding ara-C significantly increased cytology response rate (38.5% in the combination arm vs. 13.8% in the methotrexate arm; $P = .036$) and median overall survival (18.6 weeks in the combination arm vs. 10.4 weeks in the methotrexate arm; $P = .029$). At the 2009 annual meeting of the American Society of Clinical Oncology, Oh et al presented data from a retrospective study demonstrating that cytology-negative conversion following intrathecal chemotherapy predicted a statistically significant longer survival.[15]

In summary, leptomeningeal carcinomatosis as a result of metastatic gastric cancer is a rare disease. Diagnosing the disease can be clinically challenging. The prognosis of leptomeningeal disease from gastric cancer is dismal. At present, intrathecal chemotherapy remains the cornerstone in the treatment of meningeal carcinomatosis. Longer survival time could potentially be achieved with intrathecal chemotherapy, as demonstrated in some of the studies. Hence, each case needs to be considered individually when making treatment decisions. Understanding the molecular pathogenesis of the development of meningeal disease would be an important advance toward allowing us to identify potential patients at risk and treat them prophylactically.

REFERENCES

1. Wolfgang G, Marcus D, Ulrike S. LC: clinical syndrome in different primaries. *J Neurooncol* 38(2–3):103–110, 1998
2. Wasserstrom WR, Glass JP, Posner JB: Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. *Cancer* 49(4):759–772, 1982

3. Lisenko Y, Kumar AJ, Yao J, et al: Leptomeningeal carcinomatosis originating from gastric cancer: report of eight cases and review of the literature. *Am J Clin Oncol* 26(2):165–170, 2003
4. Fisher MA, Weiss RB: Carcinomatous meningitis in gastrointestinal malignancies. *South Med J* 72(8):930–932, 1979
5. Lee JL, Kang YK, Kim TW, et al: Leptomeningeal carcinomatosis in gastric cancer. *J Neurooncol* 66(1–2):167–174, 2004
6. Giglio P, Weinberg JS, Forman AD, et al: Neoplastic meningitis in patients with adenocarcinoma of the gastrointestinal tract. *Cancer* 103(11):2355–2362, 2005
7. Sze G, Soletsky S, Bronen R, et al: MR imaging of the cranial meninges with emphasis on contrast enhancement and meningeal carcinomatosis. *AJNR Am J Neuroradiol* 10(5):965–975, 1989
8. Straathof CS, de Bruin HG, Dippel DW, et al: The diagnostic accuracy of magnetic resonance imaging and cerebrospinal fluid cytology in leptomeningeal metastasis. *J Neurol* 246(9):810–814, 1999
9. Yamada T, Furukawa K, Yokoi K, et al: Case of meningeal carcinomatosis with gastric cancer which manifested meningeal signs as the initial symptom: the palliative benefit of radiotherapy. *J Nippon Med Sch* 75(4):216–220, 2008
10. Haba T, Kitoh C, Takeshita H, et al: [Case of gastric cancer associated with acanthosis nigricans and meningeal carcinomatosis]. *Gan No Rinsho* 29(8): 927–930, 1983
11. Usui N, Ogawa M, Inagaki J, et al: [Case report of meningeal carcinomatosis of gastric cancer successfully treated with intrathecal and systemic chemotherapy]. *Gan To Kagaku Ryoho* 12(1):155–159, 1985
12. Liaw CC, Ng KT, Huang JS, et al: Meningeal carcinomatosis from solid tumors: clinical analysis of 42 cases. *J Formos Med Assoc* 91(3):299–303, 1992
13. Bokstein F, Lossos A, Siegal T: Leptomeningeal metastases from solid tumors: a comparison of two prospective series treated with and without intra-cerebrospinal fluid chemotherapy. *Cancer* 82(9):1756–1763, 1998
14. Kim DY, Lee KW, Yun T, et al: Comparison of intrathecal chemotherapy for leptomeningeal carcinomatosis of a solid tumor: methotrexate alone versus methotrexate in combination with cytosine arabinoside and hydrocortisone. *Jpn J Clin Oncol* 33(12):608–612, 2003
15. Oh S, Kim S, Kwon H, et al: Leptomeningeal carcinomatosis of gastric cancer: multicenter retrospective analysis of 54 cases. *J Clin Oncol* 27 (suppl; abstr e15658), 2009
16. Gonzalez-Vitale JC, Garcia-Bunuel R: Meningeal carcinomatosis. *Cancer* 37(6):2906–2911, 1976
17. Taillibert S, Laigle-Donadey F, Chodkiewicz C, et al: Leptomeningeal metastases from solid malignancy: a review. *J Neurooncol* 75(1):85–99, 2005

Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Address correspondence to: Yixing Jiang, MD, PhD, Penn State Hershey Cancer Institute, 500 University Drive, Hershey, PA 17033. Phone: (717) 531-8678; Fax: (717) 531-5076 E-mail: yjiang@hmc.psu.edu